

REMARKS

Claim Status

The active claims in this case are claims 38-46. Each of claims 38 and 39 is amended to replace "comprising" with --wherein the method comprises-- as helpfully suggested by the Examiner. Claims 34, 36 and 37 are cancelled. As noted by the Examiner the amendments to claim 34 in the preliminary amendment dated 7 July 2003 were not properly marked. Applicants have therefore cancelled claim 34 (and dependant claims 36 and 37) and rewritten them as new claims 44-46. Claims 41-43 have been amended to recite "said gene encoding said modified Cry3Bb* polypeptide". No new matter has been introduced into the claims.

Amendments to the Drawings and Specification

FIG. 17A-C and the specification at page 58, lines 1-6 have been amended to add sequence identifiers to the corresponding sequences that are referenced therein to fully comply with the sequence rules.

Objections to Claims 34 and 38-39

Claim 34 was objected for the term "comprising". In response, new claim 44 (which replaces claim 34) has been amended to include the phrase "wherein the method comprises" as helpfully suggested by the Examiner. Similarly, claims 38-39 were objected for the term "comprising". In response, claims 38-39 have been amended to include the phrase "wherein the method comprises" as helpfully suggested by the Examiner.

AMENDMENTS TO THE DRAWINGS:

Please amend FIG. 17A-C as shown in the enclosed marked-up versions, wherein the additions of --SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112 and SEQ ID NO:113-- are shown in red. A complete set of replacement FIGS. 1-17 is provided as an appendix to this amendment.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 34 and 36-43 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner indicated that the phrase “one or more point mutations ... Lys189 to Gly” in claims 34 and 38-39 or the phrase “further comprises the amino acid substitutions ... Gln348 to Arg” in claims 37-39 and 40 were not supported in the instant specification or the originally filed claims. In response, Applicants note that support for the phrases can be found throughout the instant specification, especially in Table 2, pages 16-20, in paragraph 2.1, page 29, and paragraph 4.5, page 67. Particularly, all of the claimed amino acid substitutions are listed in Table 2, pages 16-20. Applicants also note that the instant application is a divisional of then co-pending application Serial No. 09/427,770, subsequently issued as U.S. Patent No. 6,620,988. The same phrases have been approved in 09/427,770 (now US 6,620,988), *see e.g.* claims 1 and 6.

The substitutions described in claim 34 (now new claim 44) and claims 38-43 and new claim 46 are clearly described in Table 2. In view of the teachings in the specification, one of ordinary skill would understand that combining the substitutions present in a first variant with the substitutions present in a second variant would yield a variant protein exhibiting improved toxin activity at least as great as the improvement observed in either the first or the second variant. For example, variant 11224 (described in Table 2 of the specification) exhibits an H231R substitution and a five-fold increase in activity over the native protein (see Table 2). Variant 11228 exhibits the combination of S311L, N313T, and E317K substitutions and a 4.1 fold increase in activity over the native protein. Combining all four of these substitutions together into a single variant 11231, results in a protein exhibiting a 7.9 fold increase in bioactivity over the native protein.

Another example, also presented in Table 2, provides variant 11032 exhibiting a D165G substitution and a 3.1 fold increase in activity over the native protein. Variant 11231 exhibits the combination of substitutions comprising H231R, S311L, N313T, and E317K and a 7.9 fold increase in activity over the native protein. Combining all of the variations in variant 11231 with the single variation in variant 11032 to produce variant 11098, results in a variant Cry3Bb* protein exhibiting a 7.9 fold increase in activity over the native protein.

It is believed that the subject matter, therefore, of Claims 38-46 is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 41-43 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The Examiner indicated that the recitation of “a gene encoding a modified Cry3Bb* polypeptide” is indefinite as to whether the gene is the same one with which the parent plant was transformed or if the claimed seed or plant comprises some other modified Cry3Bb* polypeptide. In response, claims 41-43 have been amended to recite “said gene encoding said modified Cry3Bb* polypeptide”.

Double Patenting Rejections

Claims 34 and 36 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 14 of U.S. Patent No. 6,501,009. Claims 34 and 36-43 were also rejected under the judicially created doctrine of obviousness-type

double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 6,620,988. In response, Applicants hereby submit a terminal disclaimer to overcome the rejections.

Conclusion

Applicants include a fee transmittal form to cover the fee associated with a terminal disclaimer (\$130). Should any additional fees be required for any reason relating to this document, the Commissioner is authorized to deduct the fees from Howrey Simon Arnold & White, LLP Deposit Account No. 01-2508/11792.0218.DVUS01.

Respectfully submitted,



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ALIGNMENT OF CRY3 SEQUENCES

(Numbered according to Cry3BB)

(alpha helices underlined, beta sheets marked with + + +'s)

| | 1 | 10 | 20 | 30 | 40 |
|----------|--|------------|---------|----|----|
| CRY3C: | MNPNNRSEHDTIKATENNEVSNNHAQYPLADTP | - - | TLEELNY | | |
| CRYCBB2: | MNPNNRSEHDTIKVTPNSELPTNHNQYPLADNP | NPSTLEELNY | | | |
| CRY3BB: | MNPNNRSEHDTIKVTPNSELQTNHNQYPLADNP | NPSTLEELNY | | | |
| CRY3BA: | MIRMGGRKMNPNNRSEYDTIKVTPNSELPTNHNQYPLADNP | NPSTLEELNY | | | |
| CRY3A: | MIRKGGGRKMNPNNRSEHDTIKTTENNEVPTNHVQYPLAETPNPTLED | LN | | | |

| | 50 | 60 | 70 | 80 | 90 |
|----------|--|-----------------------------------|----------------------------|------------|----|
| CRY3C: | KEFLRRTTDNNVEALDSSTTKDAIQKGISIIGDLLGVVGF | FPYGGALVSFY | | | |
| CRYCBB2: | KEFLRMTEDSSTEVLN | STVKDAVGTGISVVGQILGVVGVPFAGALTSFY | | | |
| CRY3BB: | KEFLRMTEDSSTEVLN | STVKDAVGTGISVVGQILGVVGVPFAGALTSFY | | | |
| CRY3BA: | KEFLRMTADNSTEVLDSSTVKDAVGTGISVVGQILGVVGVPFAGALTSFY | | | | |
| CRY3A: | KEFLRMTADNNT | ALDSSTTK | <u>DVIQKGISVVGDLLGVVGF</u> | FPFGALVSFY | |

| | 100 | 110 | 120 | 130 | 140 |
|----------|--|--------------|------------------|-----|-----|
| CRY3C: | TNLLNTIWPGE - DPLKAFMQQVEALIDQKIADYAKDKATAELQGLKNVFK | | | | |
| CRY3BB2: | QSFLDTIWPSDADPWKAFMAQVEVLIDKKIEEYAKSKALAE | LQGLQNNFE | | | |
| CRY3BB: | QSFLNTIWPSDADPWKAFMAQVEVLIDKKIEEYAKSKALAE | LQGLQNNFE | | | |
| CRY3BA: | QSFLNAIWPSDADPWKAFMAQVEVLIDKKIEEYAKSKALAE | LQGLQNNFE | | | |
| CRY3A: | <u>TNFLNTIWPSE - DPWKAFMEQVEALMDQKIADYAKN</u> | <u>KALAE</u> | <u>LQGLQNNVE</u> | | |

| | 150 | 160 | 170 | 180 | 190 |
|----------|--|-----|-----|-----|-----|
| CRY3C: | DYVSALDSWDKTPLTLRDGRSQGRIELFSQAESHFRRSMPSFAVSGYEV | | | | |
| CRY3BB2: | DYVNALNSWKKTPLSLRSKRSQDRIRELFSQAESHFRNSMPSFAVSKFEV | | | | |
| CRY3BB: | DYVNALNSWKKTPLSLRSKRSQDRIRELFSQAESHFRNSMPSFAVSKFEV | | | | |
| CRY3BA: | DYVNALDSWKKAPVNLRSRRSQDRIRELFSQAESHFRNSMPSFAVSKFEV | | | | |
| CRY3A: | <u>DYVSALSSWQKNPVSSRNPHSQGRIELFSQAESHFRNSMPSFAISGYEV</u> | | | | |

FIG. 17A



| | 200 | 210 | 220 | 230 | 240 |
|----------|---------------------------|---------------------------|-----|-----|-----|
| CRY3C: | LFLPTYAQAANTHLLLLKDAQIYGT | DWGYSTDDLNEFHTKQKDLTIEYTN | | | |
| CRY3BB2: | LFLPTYAQAANTHLLLLKDAQVFGE | EWGYSSDVAEFYHRQLKLTQQYTD | | | |
| CRY3BB: | LFLPTYAQAANTHLLLLKDAQVFGE | EWGYSSDVAEFYHRQLKLTQQYTD | | | |
| CRY3BA: | LFLPTYAQAANTHLLLLKDAQVFGE | EWGYSSEDIAEFYQRQLKLTQQYTD | | | |
| CRY3A: | LFLTTYAQAANTHLFLLKDAQIYGE | EWGYEKEDIAEFYKRQLKLTQEYTD | | | |

| | 250 | 260 | 270 | 280 | 290 |
|----------|-----------------|----------------------------|-----------|-----|-----|
| CRY3C: | HCAKWYKAGLDKLRG | STYEEWVKFNRYRREMTLTVLDLITL | FPLYDVRTY | | |
| CRY3BB2: | HCVNWYNVGLNGLRG | STYDAWVKFNRFREMTLTVLDLIVLF | PFYDVRLY | | |
| CRY3BB: | HCVNWYNVGLNGLRG | STYDAWVKFNRFREMTLTVLDLIVLF | PFYDIRLY | | |
| CRY3BA: | HCVNWYNVGLNSLRG | STYDAWVKFNRFREMTLTVLDLIVLF | PFYDVRLY | | |
| CRY3A: | HCVKWYNVGLDKLRG | SSYESWVNFNRYRREMTLTVLDLIAL | FPLYDVRLY | | |

| | 300 | 310 | 320 | 330 | 340 |
|----------|-----------------|-----------------------------|-----------|-----|------|
| CRY3C: | TKGVKTELTRDVLTD | PIVAVNNMNGYGTTFSNIENYIRKPHL | FDYLHAIQ | | |
| CRY3BB2: | SKGVKTELTRDIFTD | PIFSLNTLQEYGPTFLSIENSIRKPHL | FDYLQIGIE | | |
| CRY3BB: | SKGVKTELTRDIFTD | PIFSLNTLQEYGPTFLSIENSIRKPHL | FDYLQIGIE | | |
| CRY3BA: | SKGVKTELTRDIFTD | PIFTLNALQEYGPTFSSIENSIRKPHL | FDYLRGIE | | |
| CRY3A: | PKEVKTELTRDVLTD | PIGVNNLRGYGTTFSNIENYIRKPHL | FDYLHRIQ | | |
| | +++++ | | | | ++++ |

| | 350 | 360 | 370 | 380 | 390 |
|----------|-----------------|------------------------------|---------|-------|-----|
| CRY3C: | FHSRLQPGYFGTDSF | NYWSGNYVSTRSSIGSDEIIRSPFYGNK | STLDVQN | | |
| CRY3BB2: | FHTRLQPGYSGKDSF | NYWSGNYVETRPSIGSSKITSPFYGDK | STEPVQK | | |
| CRY3BB: | FHTRLQPGYFGKDSF | NYWSGNYVETRPSIGSSKITSPFYGDK | STEPVQK | | |
| CRY3BA: | FHTRLRPGYSGKDSF | NYWSGNYVETRPSIGSNDTITSPFYGDK | SIEPIQK | | |
| CRY3A: | FHTRFQPGYYGNDSF | NYWSGNYVSTRPSIGSNDIITSPFYGNK | SSEPVDN | | |
| | +++++ | +++++ | +++++ | +++++ | +++ |

| | 400 | 410 | 420 | 430 |
|----------|----------------|-------------------------------|---------|-------|
| CRY3C: | LEFNGEKVFRANGN | LAVWPVGTGGTKIHSGVTKVQFSQYND | RKDEVRT | |
| CRY3BB2: | LSFDGQKVYRTIAN | TDVAWPNG---KIYFGVTKVDFSQYDDQ | KNETST | |
| CRY3BB: | LSFDGQKVYRTIAN | TDVAWPNG---KVYLGVTKVDFSQYDDQ | KNETST | |
| CRY3BA: | LSFDGQKVYRTIAN | TDIAAFPDG---KIYFGVTKVDFSQYDDQ | KNETST | |
| CRY3A: | LEFNGEKVYRAVAN | TNLAVWPSA----VYSGVTKVEFSQYNDQ | TDEAST | |
| | +++ | +++++ | ++++ | +++++ |

FIG. 17B



| | 440 | 450 | 460 | 470 | 480 |
|----------|---|-------|-----|-----|--------|
| CRY3C: | QTYDSKRNVGIV-FDSIDQLPPITTTDESLEKAYSHQLNYVRCFLLQGGR | | | | |
| CRY3BB2: | QTYDSKRNGHVGAQDSIDQLPPETTTDEPLEKAYSHQLNYAECFLMQDRR | | | | |
| CRY3BB: | QTYDSKRNGHVSAQDSIDQLPPETTTDEPLEKAYSHQLNYAECFLMQDRR | | | | |
| CRY3BA: | QTYDSKRYNGYLGAQDSIDQLPPETTTDEPLEKAYSHQLNYAECFLMQDRR | | | | |
| CRY3A: | QTYDSKRNVGAVS-WDSIDQLPPETTTDEPLEKGYSHQLNYVMCFLMQGSR | | | | |
| | ++++ | +++++ | | | ++++++ |

| | 490 | 500 | 510 | 520 | 530 |
|----------|--|-------|------|-----|--------|
| CRY3C: | GIIPVFTWTHKSVDFYNTLDSEKITQIPFVKAFILVNSTSVVAGPGFTGG | | | | |
| CRY3BB2: | GTIPFFTWTWTHRSVDFNTIDAEDITQLPVVKAYALSSGASIIIEGPGFTGG | | | | |
| CRY3BB: | GTIPFFTWTWTHRSVDFNTIDAEDITQLPVVKAYALSSGASIIIEGPGFTGG | | | | |
| CRY3BA: | GTIPFFTWTWTHRSVDFNTIDAEDITQLPVVKAYALSSGASIIIEGPGFTGG | | | | |
| CRY3A: | GTIPVLTWTHKSVDFNMDSKKITQLPLVKAYKLQSGASVVAGPRFTGG | | | | |
| | ++++++ | +++++ | ++++ | | ++++++ |

| | 540 | 550 | 560 | 570 | 580 |
|----------|---|--------|-------|-------|--------|
| CRY3C: | DII-KCT-NGSGLTLYVTPAPDLTYSKTYKIRIRYASTSQVRFGIDLSY | | | | |
| CRY3BB2: | NLLFLKESSNSIAKFKVTL-NSAALLQRYRVIRIRYASTTNLRLFVQNSNN | | | | |
| CRY3BB: | NLLFLKESSNSIAKFKVTL-NSAALLQRYRVIRIRYASTTNLRLFVQNSNN | | | | |
| CRY3BA: | NLLFLKESSNSIAKFKVTL-NSAALLQRYRVIRIRYASTTNLRLFVQNSNN | | | | |
| CRY3A: | DII-QCTENGSAATIIYVTPD--VSYSQKYRARIHYASTSQITFTLSLDGA | | | | |
| | ++++++ | ++++++ | +++++ | +++++ | ++++++ |

| | 590 | 600 | 610 | 620 | 630 |
|----------|--|-------|-------|-------|-------|
| CRY3C: | THSISYFDKTMKGNLTLYNSFNLSVSRPIEISG-GNKIGVSVGGIGSG | | | | |
| CRY3BB2: | DFIVIIYINKTMNIDDLTYQTFDLATTNSNMGFSGDTNELIIGAESFVSN | | | | |
| CRY3BB: | DFLVIYINKTMNKDDDLTYQTFDLATTNSNMGFSGDKNELIIGAESFVSN | | | | |
| CRY3BA: | DFLVIYINKTMNIDGDLTYQTFDFATSNSNMGFSGDTNDFIIGAESFVSN | | | | |
| CRY3A: | PFNQYYFDKTINKGDTLYNSFNLSFSTPFELSG--NNLQIGVTGLSAG | | | | |
| | ++++++ | +++++ | +++++ | +++++ | +++++ |

| | 640 | 650 |
|----------|----------------------------------|-----|
| CRY3C: | DEVYIDKIEFIPMD (SEQ ID NO: 109) | |
| CRY3BB2: | EKIYIDKIEFIPVQL (SEQ ID NO: 110) | |
| CRY3BB: | EKIYIDKIEFIPVQL (SEQ ID NO: 111) | |
| CRY3BA: | EKIYIDKIEFIPVQ (SEQ ID NO: 112) | |
| CRY3A: | DKVYIDKIEFIPVN (SEQ ID NO: 113) | |
| | +++++ | |

FIG. 17C